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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,487	YAN ET AL.	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84,85,87-92 and 94-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84, 85, 87-92 and 94-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 84, 85, 87-92 and 94-107, are pending in the instant application and are the subject of the Office Action below.

Maintained Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 84, 85, 87-92 and 94-107, under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is maintained in modified form due to Applicants' amendments to the claims. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As was stated previously by the Examiner, the written description requirement is distinct from the enablement requirement; this was first pointed out by the court in *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), and clarified in *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). The issue of whether the claimed subject matter is adequately supported/described by the specification, is a question of fact. *Id.* at 1563, 19 USPQ2d at 1116.

When considering whether the claimed subject matter complies with the written description requirement, Applicants' disclosure should be read in light of the knowledge possessed by those skilled in the art.

> "[T]he disclosure in question must be read in light of the knowledge possessed by those skilled in the art, and that knowledge can be established by affidavits of fact composed by an expert, and by referencing to patents and publications available to the public..."

In re Lange, 644 F.2d 856, 863, 209 USPQ 288, 294. *See also, In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Applicants enjoy the presumption that their patent application is valid and all statements contained therein are accurate; it is the PTO's burden to demonstrate why any of Applicants claims should be rejected or why any of Applicant's statements should be doubted.

> "it is incumbent upon the Patent Office, whenever a rejection... is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370. If successful in presenting such evidence and argument, the burden then shifts to the Applicant to provide evidence that would convince one to the contrary.

The Invention in General

A component of Applicants' invention is directed to a method for screening inhibitors of an enzyme (class of enzyme) involved in the progression of Alzheimer's disease (AD). Applicants provide a clear and succinct background of the invention by detailing certain biochemical pathways in the formation of the plaques responsible for AD. An origin of these plaques is the amyloid protein precursor (APP), which when first processed by an enzyme having β-secretase activity, followed by an enzyme having γ-secretase activity, causes the formation of a 40/42 amino acid peptide plaque know as Aβ.

Accordingly, the development of methods for identifying compounds that might one day serve as potential β-secretase inhibitors are undoubtedly needed by the biomedical community in order to accelerate the development of AD drug candidates. As Applicants suggest, such a demand would benefit from the identification of a substrate that is more sensitive to the activity of β-secretase for use in an assay in identifying and characterizing potential inhibitors/drug candidates.

The Claimed Invention

The claimed invention (*e.g.*, claim 84), has been amended, and is directed to a method for assaying for a modulator of β-secretase activity comprising contacting: (i) a peptide having β-secretase activity, with (ii) a peptide/substrate of the generic formula N-P_1-P_1'-V, wherein the amino acid P_1 is defined as Y, L and F, and P_1' is defined as E, A and D.

Certain narrower embodiments of the claimed invention are presented in various dependent claims. Some of these claims further limit the P_1 and/or P_1' amino acids in the substrate sequence; other claims limit certain other aspects, including but not limited to the claimed labels, the length of the substrate, the presence of a quenching moiety, the polypeptide with the β-secretase activity, and assay milieu.

The Supporting Disclosure

Applicants' supporting disclosure contains numerous embodiments of the invention. Pages 3 through 5 list a number of different chemical genera of a peptide fragment comprising various groups of amino acids that have a scissile bond when reacted with a protein having β-secretase activity. For example, on page 3, the peptide fragment is defined by the genus P_2P_1-P_1'P_2', wherein P_2 is defined as a charged amino acid, a polar amino acid or an aliphatic amino acid but is not an aromatic amino acid, P_1 is an aromatic amino acid or an aliphatic amino acid but not a polar amino acid or a charged amino acid; P_1' is a charged amino acid, or aliphatic amino acid, or a polar amino acid but is not an aromatic amino acid; and P_2' is an uncharged aliphatic polar amino acid or an aromatic amino acid but not a charged amino acid; wherein the peptide is cleaved between P_1 and P_1' by two certain human aspartyl proteases, and has certain other provisos.

Certain other embodiments further limit an aspect of the invention by describing the peptide fragments as certain sequence encoded by $P_4P_3P_2P_1$-P_1'P_2'P_3', and list the possible amino acids that could by used at the corresponding P values. Applicants provide some guidance with respect to the preferred P values, and list those values on page 5. On page 6, Applicants describe particular sequences that are preferred peptides of the present invention by SEQ ID NO.

The disclosure describes a number of substrates encompassed by the claimed chemical genus that produce β-secretase activity, and conveniently groups these substrates by sequence

similarity to illustrate certain trends or correlations (Tables 2-5, and description thereof). Following Table 3 on pages 21-23, the disclosure describes the particular substitutions and the resulting effects on activity (objective statements; not an explanation of the physicochemical properties as it relates to the enzyme system). The discussion following Table 5 on pages 25 and 26 is similar. The disclosure does, however, indicate on page 26 that extension of the N-terminal region of a particular peptide fragment is expected to enhance activity.

On pages 28 and 29, the disclosure describes the amino acids by their well-known characteristics and explains hydropathic indexing. In particular, the specification states:

> "It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of a resultant protein or peptide, which in turn defines the interaction of that protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics (Kyte & Doolittle, *J. Mol. Biol.*, 157(1):105-132, 1982, incorporated herein by reference). Generally, amino acids may be substituted by other amino acids that have a similar hydropathic index or score and still result in a protein with similar biological activity *i.e.*, still obtain a biological functionally equivalent protein or peptide. In the context of the peptides of the present invention, a biologically functionally equivalent protein or peptide will be one which is still cleaved by β-secretase at a rate exceeding the rate of cleavage of a nature [*sic*] APP peptide comprising SEQ ID NO: 20."

Applicants' disclosure, page 29, lines 6-18.

Table 6 lists Applicants exemplary amino acids that they consider to be useful at the positions P_4, P_3, P_2, P_1, P_1', P_2', P_3' and P_4'. It appears that the selection of these amino acids is based, in-part, on certain working examples (*i.e.*, tested peptide fragments having β-secretase activity), amino acids that are listed as equivalents to the working examples based on the hydropathic index, and possibly certain prophetic examples as listed on pages 30 and 31. It further appears that the combination of individual amino acids at each of the P values that form the claimed P_2P_1-P_1'P_2' peptide fragment are independently selected.

Additionally, the description discloses a number of other embodiments relevant to Applicants' invention, such as labels, fusion proteins, detection schemes, transgenic animals, certain laboratory preparation techniques, etc.

The State of the Art

A number of reference are relied upon as factual support in challenging certain statements made in the instant application and as a basis for rejecting the claims for lacking written description. For example, Gruninger-Leitch *et al.* ("Leitch"), *J. Biol. Chem. 277(7)*:4687-4693 (**2002**); Majer *et al.* ("Majer"), *Protein Science 6*:1458-1466 (**1997**); Sauder *et al.* ("Sauder"), *J. Mol. Biol. 300*:241-248 (**2000**); Shi *et al.* ("Shi"), *J. Alzheimer's Disease 7*:139-148 (**2005**); and Tomasselli *et al.* ("Tomasselli"), *J. Neurochemistry 84*:1006-1017 (**2003**); taken together, suggest that Applicants were not in possession of the claimed invention at the date of filing, and further, have not provided such sufficient description to support the invention as is broadly claimed. Specifically, the art as a whole provides sufficient evidence that demonstrates that Applicants' particular N-P_1-P_1'-V species as broadly claimed, taken in combination with their supporting disclosure, the specification does not support the breadth of the claimed N-P_1-P_1'-V genus where P_1 is F, in view of the art.

Leitch discloses a comparison study between certain proteases including BACE, BACE2, cathepsin D and E, napsin A, pepsin and rennin, and teaches that BACE presents itself as an ideal target for AD treatment. In particular, Leitch teaches the specificity and activity of a number substrates that are cleavable by BACE in comparison to other proteases. Certain factors identified in Leitch's teachings would suggest that Applicants' claimed genus is unsupported by their disclosure include the following factors: i) the effects of, and importance, of amino acids further from the scissile bond of the substrate, such as P_4, P_3, P_3' and P_4'; ii) the length of the substrate required for cleavage by the BACE enzyme; and iii) certain *in vitro* and *in vivo* differences in activity, wherein any single factor may or may not be coupled to any other factor(s). Table 1 illustrates the effects of certain substrate mutations compared to the Swedish type APP substrate. A single amino acid mutation at P1' of the Swedish mutant APP β-cleavage site (NL-D → NL-A), results in an 84% drop in activity. Even more surprisingly, the P4K substrate which differs from the Swedish mutant APP β-cleavage site (NL-D) by a single amino acid at P_4, yet retains the same P_2P_1-P_1'P_2' sequence, results in a 50-fold drop in activity (Table 1 on page 4689). These mutations and effects are relevant to the breadth and subject matter of Applicants' claims, and do not appear to be remedied by the art or Applicants' disclosure.

Similar to Applicants' approach (see pages 20-30 of the instant application), Leitch progressively optimizes certain substrates based on observed preferences in BACE substrates (pages 4690-4691). Although Applicants have optimized their sequences based on insulin and ubiquitin, such studies and a general reference to the hydropathic indexing of substrates does little to provide a structure-activity nexus for linking the broad array of species to the relatively large claimed genus. Leitch demonstrates a number of amino acids substitutions for certain positions within the cleavable peptide substrate, and reveals that certain amino acid combinations appear to be interdependent.[1] Leitch also teaches that the *in vivo* and *in vitro* differences can affect activities, possibly due to an orientation effect and the cell lumen (page 4692), and can be further complicated by the size of the substrate (page 4693).

Given the fact that the amino acid substitution effects are not necessarily additive, and that drastic effects in activity can be observed by changing amino acids either in the P_2P_1-$P_1'P_2'$ region, support for Applicants' genus is reasonably challenged by the teaching of Leitch. As a result of each of these factors, considered independently or as having a cumulative effect on the substrate/enzyme relationship, one of ordinary skill in the art would doubt that Applicants had adequately described the invention as broadly claimed.

Tomasselli also reports experimental findings that demonstrate that the claimed genus is not supported by the disclosed species because of amino acid interdependence and *in vitro* and *in vivo* differences in activity:

> "Enzyme subsites are interdependent and occupancy of a subsite by two 'well tolerated', but different amino acids, may differentially influence the amino acid preferences at the other subsites."

Tomasselli at page 1014, column 1; and again regarding the interdependence of amino acids:

> "Our findings indicate that amino acid preference at a specific site has to be regarded in the context of the peptide sequence rather than of maximal statistical occurrence of that amino acid at that specific position in the substrate. *A P1 Leu may be highly preferred in a library of peptide substrates, but Tyr is optimal at this position in our best substrate because of its interdependence upon its neighboring P-site substituents.* We have produced an optimal BACE1 substrate by systematic changes in individual

[1] Leitch teaches that "the hydroxylamino acids Thr and Ser were found at position P_2 only in combination with Ser at P_1'."

> P-sites considered globally with respect to the overall sequence, and by N-terminal extension of the peptides with the naturally occurring APP sequence."

Id. at page 1014, column 2 (emphasis added). Regarding Tomasselli's "systematic" approach, however, neither Applicants nor Tomasselli provide sufficient description to link all of the claimed species to the genus. Instead, one of ordinary skill in the art would consider the approaches of Leitch and Turner to be "systematically" different, but still systematic. For example, Shi discloses a BACE substrate identified by a library approach that is about 3-4 fold more scissile than that disclosed by Tomasselli (Shi at page 141, column 2). Although certain approaches may be better served for identifying a few particular species, Applicants' and Tomasselli's approaches do not sufficiently describe the breadth of the genus as claimed.

Majer discloses a series of compounds produced through a systematic approach for optimizing inhibitor polypeptides to cathepsin D, an aspartic protease. Similar to optimizing BACE substrates with a scissile bond, a number of factors are important in substrate/inhibitor optimization, including but not limited to, hydropathy, orientation of the amino acid side chains, backbone configuration, hydrogen bonding, side chain length, and a number of subsite considerations, such as steric interactions, solvation, etc. Majer also teaches that there are additional important considerations besides the P_2P_1-$P_1'P_2'$ amino acid residues (pages 1458-1465), and that amino acid substitutions are not necessarily additive (page 1462).

Many of the claimed amino acid substitutions do not necessarily follow from any disclosure, or the corresponding systematic approaches. One sequence that only differs from Applicants' most active substrate (SY-EV) is the sequence GY-EV as disclosed in Sauder (see Figure 4 on page 246, and description thereof on page 245), however, this sequence has drastically reduced in activity in comparison. Based on the hydropathic index, the single value difference between S → G is –0.4 (see page 110 of Kyte and Doolittle, *J. Mol. Biol. 157(1)*:105-132 (**1982**)). Vassar discloses that a substitution of a single amino acid to P1 of the APPwt (M → V), results in elimination of the scissile bond. Although the difference in going from M → V has a single position value difference in the hydropathic index of 2.3, the wt to Sweedish mutation has a hydropathic difference of comparable magnitude at 2.0 at P1 (Kyte at page 110).

P_2P_1-$P_1'P_2'$ Sequence	*Description*
KM-DA	APPwt
NL-DA	Swedish mutant with high increase in activity
KV-DA	lacks activity
GY-EV	low activity; the wt β'-secretase site
SY-EV	Applicants' most active sequence fragment
NF-EV	Shi's most active sequence fragment

However, it is not truly predictable from Applicants' or any other "systematic" approach, or the teachings in the art, what effects certain amino acid substitutions will have on a substrate, even if the substitution is sometimes preferred for one particular substrate, or by relying on hydropathic indexing.

Accordingly, for at least these reasons, Applicants have not adequately described the invention for the breadth that is claimed. It thus appears that Applicants were not in possession of the claimed invention at the time the application was filed, the structure-function relationship between the protease and the scissile substrates have not been adequately set forth, and that Applicants' species do not support the claimed genus.

Applicants' Analysis of the Claimed Subject Matter and Descriptive Support in their Application

Applicants correctly state that their currently claimed genus represents a number of substrates comprising six different amino acid sub-sequences. Applicants point to their specification and identify a table that lists their preferred amino acids for substrates having the sequence P_4-P_3-P_2-P_1-P_1'-P_2'-P_3'-P_4'. Overall, Applicants appear to be of the opinion that the path from the broadest genus to the claimed genus has clearly been set forth, and that where any bit of uncertainty exists, it is within the realm of routine determination:

> "While the genus may seem large in some contexts, ***it is a pittance in the fields of chemistry and molecular biology, where automated synthesis techniques, recombinant techniques, and high throughput screening techniques (to name just a few) abound, making manipulation and testing of large numbers of molecules a common occurrence.*** In view of

> the guidance in the specification and the known properties of conservative amino acid substitutions, the total number of possible species is less than what the Patent and Trademark Office routinely issues in connection with an allowance of a typical genus claim in a specification directed to traditional organic chemical pharmaceuticals. The written description training materials approve of this practice, e.g., by approving of claims to a genus of biomolecules by "percent identity" to a reference sequence, together with a limitation of function."

Reply, page 9, within first paragraph (emphasis added).

Applicants continue to assert that certain post-filing publications demonstrate that Applicants have support for the claimed genus, and make reference to U.S. Patent No. 7,132,401 (Table 3) PCT Publication No. WO 02/094985 (page 41, lines 19-25) and PCT Publication No. WO 2004/099376 (page 7, lines 21-24).

However, what is more apparent, is that the preferred genus from Table 6 wherein the genus sequence is P_4-P_3-P_2-P_1-$P_{1'}$-$P_{2'}$-$P_{3'}$-$P_{4'}$, effectively discloses 9,878,400 amino acid substrates, while Applicants have only presented four working examples within the scope of claimed genus N-P_1-E-V. It is also apparent that of the working examples, none the substrates tested have less than 10 amino acids, and all have limited variability before P_2 and after $P_{2'}$.

Applicants' reliance on the art of other research efforts in this field that were made publicly available after Applicants' filing date, which shows the success of substrate species directed to P1 amino acids that are M, F and H, is not persuasive. Applicants must show at the time of filing that they were in possession of the claimed invention, not wait to see what others have discovered and selectively trim their own genus down by an order of 10^6. For example, if one were to inquire whether the ordinary practitioner in the art were to look at: 1) Applicants' broadly described genus, such as Table 6; 2) any genus that Applicants have described as "preferred" and "more preferred"; 3) the working examples; 4) Applicants teachings with regard to conservative amino acid substitutions and other methods for extrapolating amino acid substitutions based on the working examples; and 4) the relevant art as a whole; and then arrive at the claimed genus of compounds, the answer would be "no." Based on the comparison of the four working examples to the 9,878,400 amino acid substrates that can be generated from Table 6 of the specification, taken in consideration with the experimental findings in the art and the fact

that the function of one substrate does not extrapolate to the development of other substrates, one of ordinary skill in the art would disagree with Applicants' position.

Applicants Allege the Claims are Limited to Functional Peptides

Applicants assert "that it is not the function of the claims to specifically exclude possible inoperative substrates, and undue experimentation depends on whether the number of inoperative substrates becomes significant," and cites Atlas Powder as the authority.

The Examiner agrees, however, the issues is whether the current scope of the claim meets that standard. The current scope of the claims does not meet that standard.

Applicants further contend that the Leitch reference has been misapplied to their invention, stating that the art is not germane to the to the written description requirement of the claims (page 10 of Applicants' reply), but appear to believe that certain limited successes achieved by Leitch are supportive of Applicants' possession of the additional species, in addition to other art made of record in support of the Examiner's arguments.

The Examiner disagrees. Leitch is relevant because Leitch demonstrates that, like the claimed invention, BACE proteins can only tolerate so much change in the amino acid substitutions made surrounding/encompassing the cleavable substrate. Leitch further teaches that amino acid substitutions based on certain extrapolations fail; many success are noted to occur without pattern or scientific explanation ("[a] new substrate...was identified by serendipity"; Lietch, in the Abstract). And interestingly, although Applicants' acknowledge that Leitch has had certain successes with certain modified BACE substrates, no sequence in Leitch has had the claimed N-P_1-E-V sequence.

Applicants contend that the other three amino acid sequences would only require routine experimentation based on their work, and state that there is a reasonable expectation that "carrying out the methods described in the specification will be successful in identifying substrates that are cleaved by a human aspartyl protease." Reply, page 11.

Again, this does little to demonstrate that Applicants claimed invention was adequately described. Applicants have not adequately described, or made reference to the appropriate art, as to how one of ordinary skill in the art would utilize, for example, any of the aforementioned tools, to arrive at that genus. Barring the hindsight privilege that Applicants have at this point

for identifying certain other amino acid residues that produce a scissile bond within their claimed sequence, namely M, F and H for position P_1, there is insufficient support in Applicants' disclosure for claiming the use of these sequences. Although it is known in the art that the use of conservative amino acid substitutions, bioinformatics algorithms and structural modeling, can be successfully used in conjunction with experimental data, the art shows that there are significant limits that are relevant to the claimed genus.

On page 11, second paragraph, the Applicants contend that "these methods" are routine in the art, and suggest that this is one aspect of the possession criteria.

However, the fact that one possess a viable cleavage assay, or a diagnostic to determine if a sample substrate is amenable to BACE cleavage wherein the sequences to be tested are generated from a defined set amino acid sequences with genus, does not amount to possession of all species (or to routine experimentation, as Applicants suggest).

Applicants state:

> "[i]t is inappropriate to assert that substrates cleaved at a lower efficiency do not support the claimed genus when this measured efficiency was. determined by a comparison of cleavage of the highly efficient "Swedish mutation" substrate. Even the wild-type substrate has only 9% cleavage compared to the Swedish mutation, yet it can be used in assays."

Reply, page 12, second paragraph.

In response, this statement was never made by the Examiner. The point raised by the Examiner with regard to Leitch was to demonstrate how even in cases where a single amino acid point mutation is made in an otherwise scissile BACE substrate, drastic reductions in substrate activity are shown to occur. Simply, it is a single, yet important aspect of the art that demonstrates, in-part, that certain technical issues in obtaining compounds based on the activity of other compounds is not as straightforward as Applicants contend. For example, following a number of rounds of experiments, Leitch is able to determine that certain substrates having subsequence N-L for residues P_2-P_1 are active. A substantial basis for the discovery of successful amino acid combinations is found through experimentation, with a number of discoveries unaccounted for by methods that are based on conservative amino acid substitutions, such as interdependencies within the P_2P_1-$P_1'P_2'$ framework:

> "The P_2-P_1 library was designed to assess which amino acids other than those found in wild-type APP (Lys, Met) and Swedish mutant APP (Asn, Leu) can be accepted in the P2 and P1 positions. The Asn-Leu motif was detected several times, and Leu was also found in combination with Glu or Asp. On the other hand, neither the Lys-Met motif nor anything resembling it was ever detected, indicating that, in our in vitro assay at least, wild-type APP is not a preferred substrate for BACE. ***The Gly-Tyr motif, corresponding to the alternative cleavage site in APP (leading to $A\beta_{11-x}$), was also never detected in these experiments***.
>
> Because 22 of 25 experiments revealed Leu as the preferred P_1 residue, we generated a second library with a fixed Leu at P_1 and variable amino acids at P_2 and $P_{1'}$ positions. Asn was found as the preferred residue in P_2. From a total of 66 beads, 24 showed Asn, 14 Glu, and 12 Asp, with Gln found once. ***The hydroxylamino acids Thr and Ser were found at position P_2 only in combination with Ser at $P_{1'}$***."

Leitch, page 4690, second column (emphasis added). One of ordinary skill in the art would expect that these trends are related to all BACE substrates, including Applicants' claimed invention. Based on the working examples, the broader genus, and Applicants' other description within the application, one of ordinary skill would find that the genus excludes M, F and H at position P_1.

Regarding the differences that Applicants point to regarding the disclosures of Majer, Applicants' arguments are not persuasive. Majer, like the claimed invention, deals with enzymes that cleave peptide substrates. Regardless of the cleavage site, it is still relevant that identifying operable conservative amino acid substitutions are not necessarily routine decisions, among other variables (see discussion of Majer above). The same applies for the other references of record.

Accordingly, the rejection is maintained.

Double Patenting

The rejection of claims 84, 85, 87-92 and 94-107, under the doctrine of provisional double patenting is maintained. Applicants do not point to any alleged error in the rejection, nor do Applicants identify any distinguishable difference in the claim sets. Instead, Applicants assert that the claims of any one application will be amended at the time of the allowance.

Accordingly, the rejection is maintained.

Conclusions

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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